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Nanocatalyzed Hydrogen Isotope Exchange

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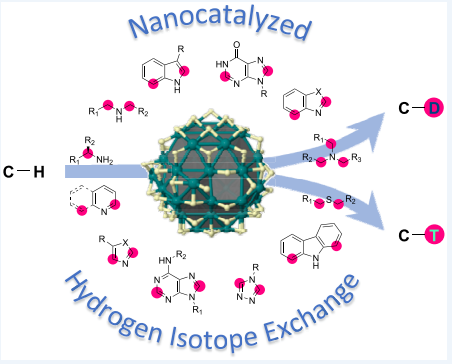
CONSPECTUS: Recently, hydrogen isotope exchange (HIE) reactions have experienced impressive development due to the growing importance of isotope containing compounds in various fields including materials and life sciences, in addition to their classical use for mechanistic studies in chemistry and biology. Tritium-labeled compounds are also of crucial interest to study the *in vivo* fate of a bioactive substance or in radioligand binding assays. Over the past few years, deuterium-labeled drugs have been extensively studied for the improvement of ADME (absorption, distribution, metabolism, excretion) properties of existing bioactive molecules as a consequence of the primary kinetic isotope effect. Furthermore, in the emergent "omic" fields, the need for new stable isotopically labeled internal standards (SILS) for quantitative GC- or LC-MS analyses is increasing. Because of their numerous applications, the development of powerful synthetic methods to access deuterated and tritiated molecules with either high isotope incorporation and/or selectivities is of paramount importance.



HIE reactions allow a late-stage incorporation of hydrogen isotopes in a single synthetic step, thus representing an advantageous alternative to conventional multistep synthesis approaches which are time- and resource-consuming. Moreover, HIE reactions can be considered as the most fundamental C−H functionalization processes and are therefore of great interest for the chemists' community. Depending on the purpose, HIE reactions must either be highly regioselective or allow a maximal incorporation of hydrogen isotopes, sometimes both. In this context, metal-catalyzed HIE reactions are generally performed using either homogeneous or heterogeneous catalysis which may have considerable drawbacks including an insufficient isotope incorporation and a lack of chemo- and/or regioselectivity, respectively.

Over the past 6 years, we have shown that nanocatalysis can be considered as a powerful tool to access complex labeled molecules (e.g., pharmaceuticals, peptides and oligonucleotides) via regio- and chemoselective or even enantiospecific labeling processes occurring at the surface of metallic nanoclusters (Ru or Ir). Numerous heterocyclic (both saturated and unsaturated) and acyclic scaffolds have been labeled with an impressive functional group tolerance, and highly deuterated compounds or high molar activity tritiated drugs have been obtained. An insight into mechanisms has also been provided by theoretical calculations to explain the regioselectivities of the isotope incorporation. Our studies have suggested that undisclosed key intermediates, including 4- and 5-membered dimetallacycles, account for the particular regioselectivities observed during the process, in contrast to the 5- or 6-membered metallacycle key intermediates usually encountered in homogeneous catalysis. These findings together with the important number of available coordination sites explain the compelling reactivity of metal nanoparticles, in between homogeneous and heterogeneous catalysis. They represent innovative tools combining the advantages of both methods for the isotopic labeling and activation of C−H bonds of complex molecules.

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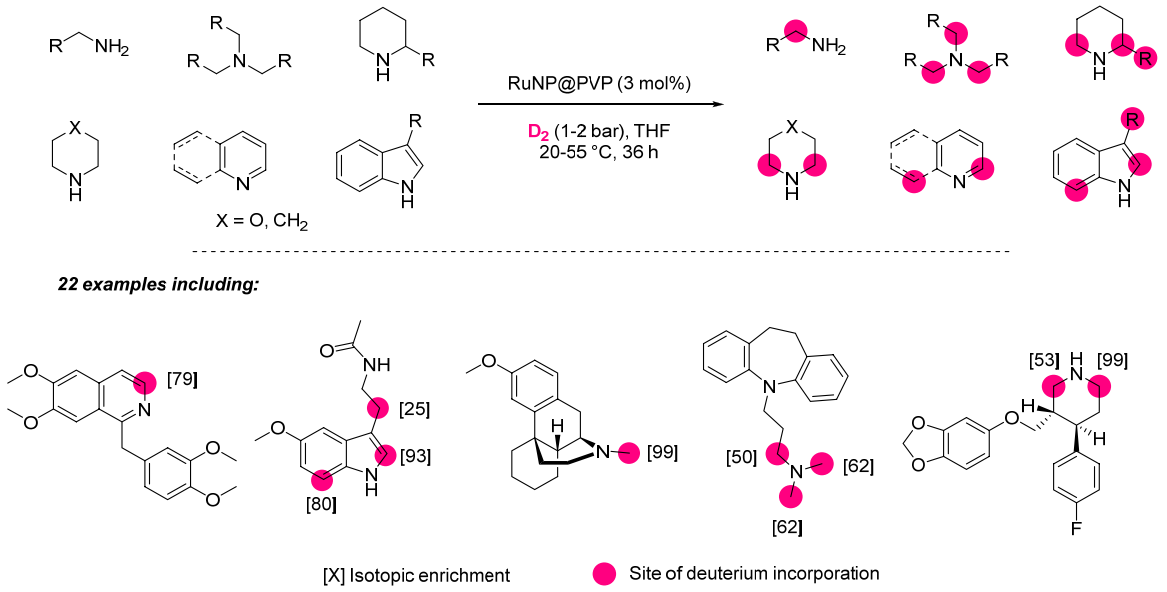

Figure 1. Scope and regioselectivity of RuNP@PVP catalyzed HIE reactions on various N-heterocycles.

Chem., Int. Ed. **2019**, *58*, 4891−4895.[2] *Nanoparticle engineering allowing the labeling of fragile nucleobases and oligonucleotides using nanocatayzed HIE.*

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1. INTRODUCTION

This Account is focused on the recent developments of nanocatalyzed hydrogen isotope exchange (HIE). For more information on HIE or nanoparticles used in this Account, recent and detailed reviews have been published.[5,6]

Hydrogen isotopes play a critical role in a large panel of scientific research areas and technological developments with huge human, economical, and societal impacts. In particular, deuterated/tritiated compounds are used (1) in the health sector as internal mass spectrometry standards or radioactive tracers which are crucial for Drug Discovery and Development,[7,8] (2) in (bio)chemistry for mechanistic studies,[9] (3) in biology in proteomics and metabolomics fields,[8] and (4) for diagnostics as MRI tracers.[10] Moreover, deuterium is the central element of the promising pharmaceutical market of "heavy drugs" with improved properties,[11] and it has been used to improve the metabolic stability of PET (positron emission tomography) diagnostic tracers[12,13] as well as to enhance the efficiency and lifetime of optoelectronic devices such as OLEDs and optical fibers.[14]

Isotopic labeling has been intensively investigated over the past decades, and numerous labeling methods are currently available. Among them, metal-mediated hydrogen isotope exchange permits the late stage labeling of compounds, thus reducing waste, time, and costs compared to conventional multistep syntheses.[5] Homogeneous catalysis allows the labeling of molecules with high selectivity under mild conditions but generally with moderate isotope incorporation, as only specific positions can be activated. On the other hand, heterogeneous catalysis gives access to high isotope incorporation but with a reduced selectivity and often requires the use of harsher conditions. To combine advantages and circumvent drawbacks of existing homogeneous and heterogeneous catalysts, the use of nanoparticles appeared recently as an attractive solution. Different types of organometallic nanoparticles (NPs) have been developed for the past 25 years.[6] Although they are not defined molecular objects, they can be made monodisperse and their size can be modulated. Regarding our work, we primarily used Ru and Ir NPs with controlled sizes between 1 and 2 nm and various surface stabilizers: polymers such as polyvinylpyrrolidone (PVP) or ligands. N-Heterocyclic carbenes (NHC) were the most promising ligands which can be soluble either in organic solvents[15] or in water[16] depending on the requirements. The synthesized NPs accommodate surface hydrides and their reactivity and selectivity can be modulated by the nature and concentration of surface ligands or by the presence of different metals (bimetallic NPs).

Following our pioneering discovery that, under an atmosphere of D_2 gas, primary amine (hexadecylamine) ligands of Ru nanoparticles were labeled and our being intrigued by this reactivity, we started our journey to the labeling world by focusing on nitrogen-containing compounds.[1] First, we were able to successfully label N−C(sp^2)−H and N−C(sp^3)−H bonds under mild reaction conditions (55 °C, 1−2 bar of D_2 gas) and using a low catalyst loading (3 mol % of RuNP@PVP, see Figure 1).

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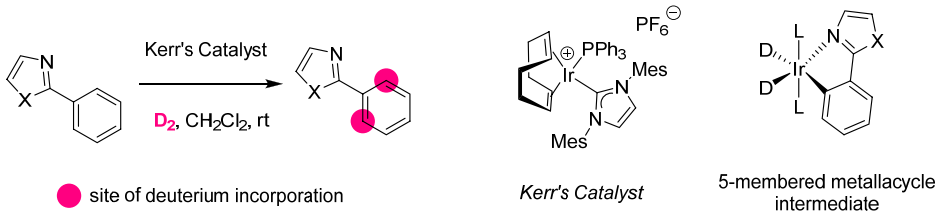

Figure 2. Homogeneous Ir(I) catalyst and its corresponding 5-membered metallacycle intermediate

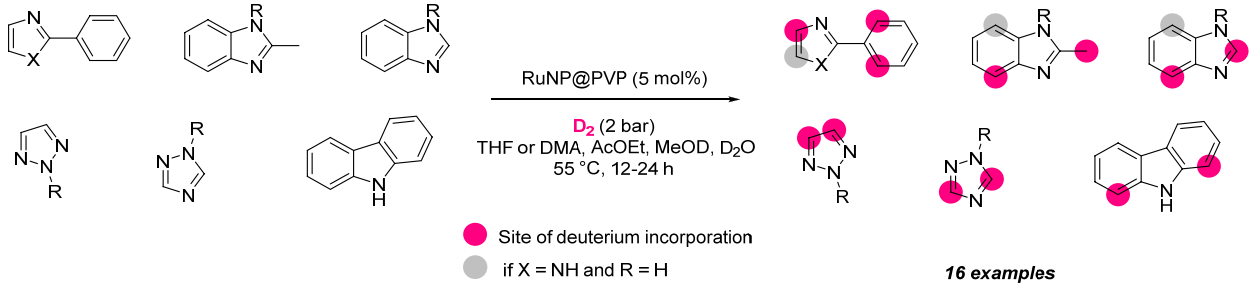

Figure 3. Scope and regioselectivity of RuNPs catalyzed HIE reactions on various N-heterocycles.

All compounds tested were obtained in good yields with high chemo- and regioselectivities combined with good to high isotopic enrichments (50−99% at the α-position of the nitrogen atom mainly). At this stage we believed that, for the vast majority of the compounds labeled, the regioselectivity was driven by the N-coordination of the substrate at the surface of the catalyst, thus leading to the labeling at the α-position of the nitrogen atom and at the β- or γ-position for indole and 2-phenylpyridine substructures through the formation of various type of metallacycles. The mild conditions used permitted the labeling of eight bioactive compounds without loss of enantiomeric purity in all cases, even if the labeling took place in close proximity to the chiral center.

2. NANOCATALYZED C(sp^2)−H ACTIVATION USING RUTHENIUM NANOPARTICLES

After our first results showing the potency of RuNPs for H/D exchange reactions on both C(sp^2)−H and C(sp^3)−H bonds, we looked forward to expand the scope of this method to relevant N-heterocyclic scaffolds and to gain an insight on the reaction mechanism. Labeling of nitrogen-containing heterocycles is indeed of substantial interest: triazoles (either 1,2,3- or 1,2,4-), imidazoles, and benzimidazoles are all widely encountered moieties in U.S. Food and Drug Administration approved drugs.[17] Oxazoles and carbazoles are also frequent substructures in medicinal chemistry or in materials science.[18]

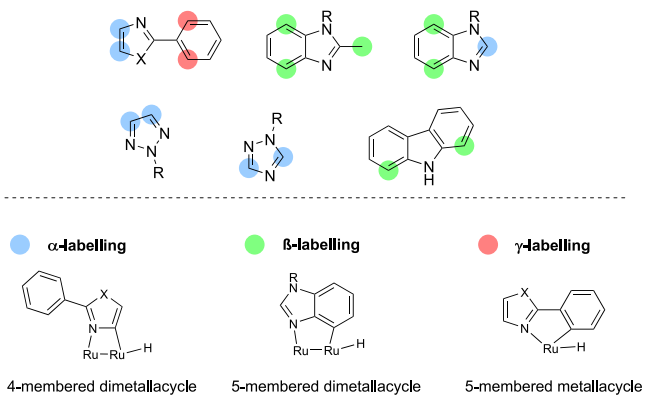

Figure 4. Key intermediates involved depending on the regioselectivity of the labeling.

In this context, homogeneous Ir(I) catalysts have been used for the selective deuteration of aromatic substituents in position 2 of oxazole and imidazole moieties with rather moderate deuterium incorporation (see Figure 2).[19,20]

Homogeneous iron and nickel catalysts have demonstrated a moderate activity for the isotopic labeling of 1,2,3-triazoles allied with only low isotopic enrichments,[21,22] whereas no broadly applicable HIE method on 1,2,4-triazoles or carbazoles have yet been described.

Using RuNP@PVP, we were able to incorporate up to five deuterium atoms at α, β, and γ positions of a nitrogen atom on a broad scope of the aforementioned N-heterocyclic substrates in a large variety of solvents (see Figure 3).[23]

Besides demonstrating the very wide scope of the application of RuNP catalysis, we were interested in understanding the reaction mechanism explaining the regioselectivity of the isotope incorporation. Theoretical calculations (DFT-PBE), using a 0.5 nm ruthenium cluster model with 1.4 H atoms *per* Ru surface atom ($Ru_{13}H_{17}$), carried out by the team of Poteau has allowed us to explain the different regioselectivities experimentally observed. It ultimately appeared that the reaction pathway (see Figure 4) involves either 4- and 5-membered dimetallacyclic key intermediates (respectively, for α and β position labeling) or a 5-membered metallacycle (γ position labeling).

Regardless of the regioselectivity of the labeling, the reaction pathway always involves an initial exothermic adsorption of the substrate through a nitrogen σ- or π-coordination (in the case of carbazoles) on a Ru atom. Then, a stabilizing agostic interaction can be established between the activated C−H bond and an adjacent Ru atom (in the case of dimetallacycles) or the same Ru atom (in the case of monometallacycles). The consecutive C−H bond breaking step always involves relatively low activation barriers (between 0.0 and 7.4 kcal·mol^{-1}, depending on the

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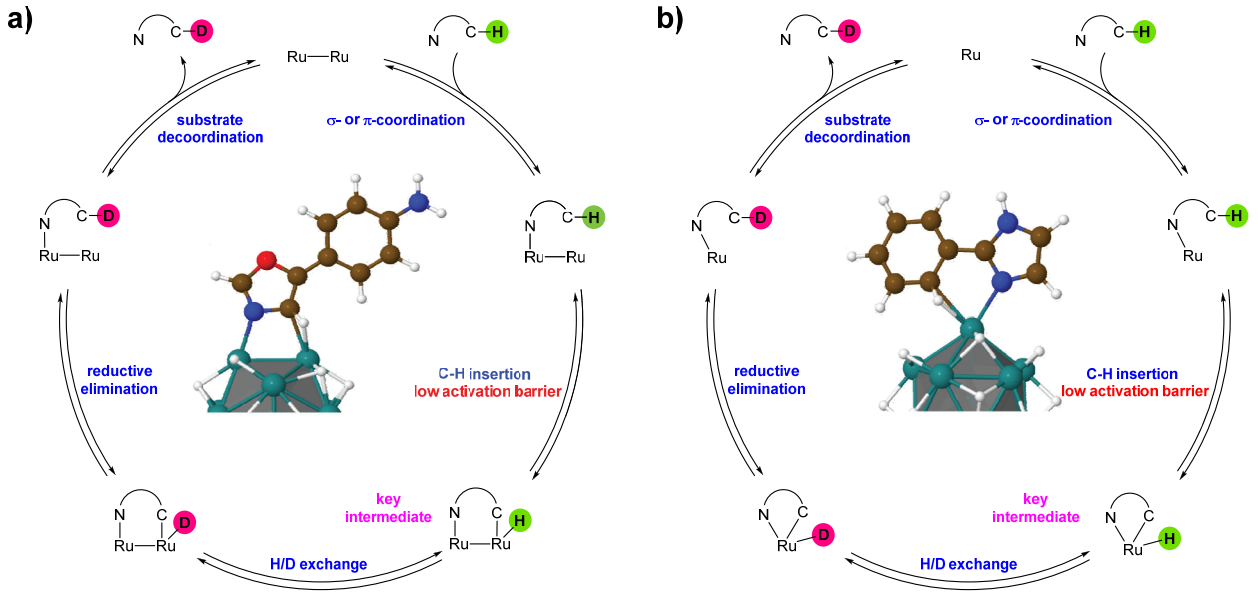

Figure 5. General mechanistic pathway for the deuterium labeling of N-heterocyclic compounds using RuNPs (a) with dimetallacyclic intermediates and (b) with monometallacyclic intermediates.

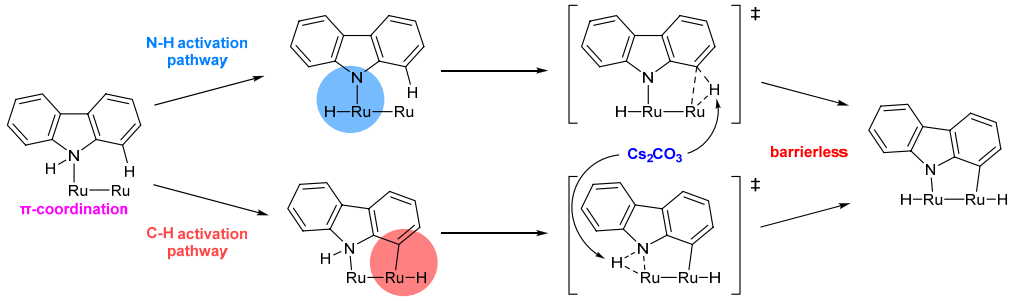

Figure 6. Two pathways explaining the β-labeling of carbazoles.

substrate). Then, due to the easy diffusion of hydrides and deuterides at the surface of the RuNPs, a barrierless H/D exchange occurs and finally the labeled compound was obtained after a formal reductive elimination (see Figure 5 for the general mechanistic pathway).

For carbazole derivatives, the nitrogen atom is only weakly coordinated to the RuNP through a π-coordination (instead of a σ-coordination for the previous mentioned heterocycles). In this case, two pathways were considered, either via the N−H activation followed by the C_1−H activation or the reverse. Calculations showed that both mechanisms were feasible although the barrier for the C−H activation step is significantly lowered if the N−H activation takes place beforehand. We then showed that, after a first C−H or N−H activation step, a Cs_2CO_3 molecule present in the close vicinity of both intermediates could efficiently abstract a hydrogen atom from the N−H or the C_1−H bond, respectively. This leads to an exothermic and barrierless X−H bond (X = N or C) breaking step leading to improved isotope incorporations (see Figure 6). It should be noted that Cs_2CO_3 may be useful for any heterocycle containing an acidic N−H group including indoles.

With the mechanistic studies in hand, we turned our attention toward the labeling of complex pharmaceuticals containing the aforementioned N-heterocycles. We obtained good isotopic enrichments over a large variety of scaffolds, thus validating our method for the preparation of stable isotopically labeled commercial drugs for LC-MS quantification (SILS) or for metabolic studies (see Figure 7).

The low C−H activation barriers calculated led us to believe that our methodology would be useful for the isotopic labeling of less stable molecules such as purine-containing nucleobase pharmaceuticals and oligonucleotides. Because of the need for such deuterated analogues as SILS in ADME (absorption, distribution, metabolism, excretion) studies, a reliable labeling method is desperately needed. Generally, deuterated and tritiated nucleobase derivatives are obtained via time- and resource-consuming multistep syntheses.[24] Only few examples of HIE reactions have been described on such substrates, either by using catalytic amounts of Pd/C in deuterated water[25] or by performing an acido-basic exchange of the 8-position of purine derivatives.[26] However, these methods require harsh conditions and are thereby limited to simple substrates. Using mild reaction conditions, D_2 gas (2 bar), and RuNP@PVP as the catalyst in deuterated water, we successfully labeled various purine derivatives with good isotopic enrichments (up to 3.9 D incorporated) over a wide pH range.[2] A wide range of complex purine-containing drugs including doxofylline, vidarabine, didanosine, adefovir, and idelalisib was efficiently deuterated.

Subsequently, nanoparticle engineering was envisioned in order to improve the solubility of the nanocatalyst in both

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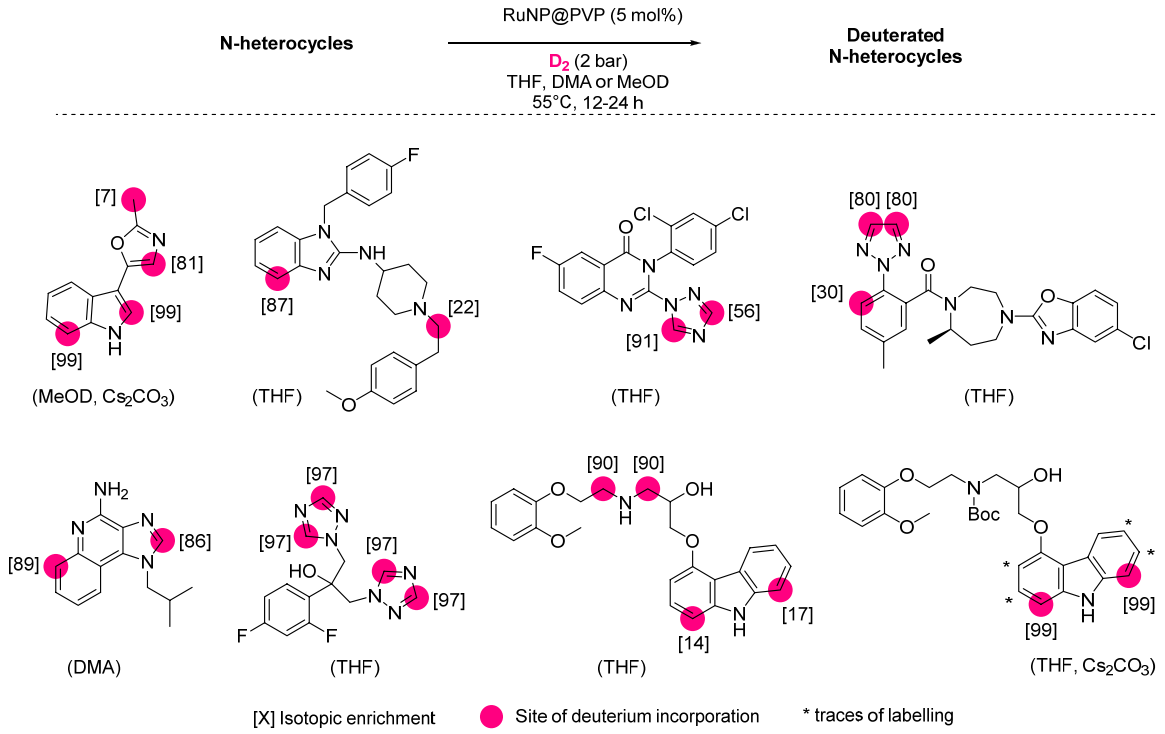

Figure 7. Deuterium labeling of complex pharmaceuticals (2 bar of D_2 gas, 55 °C, overnight).

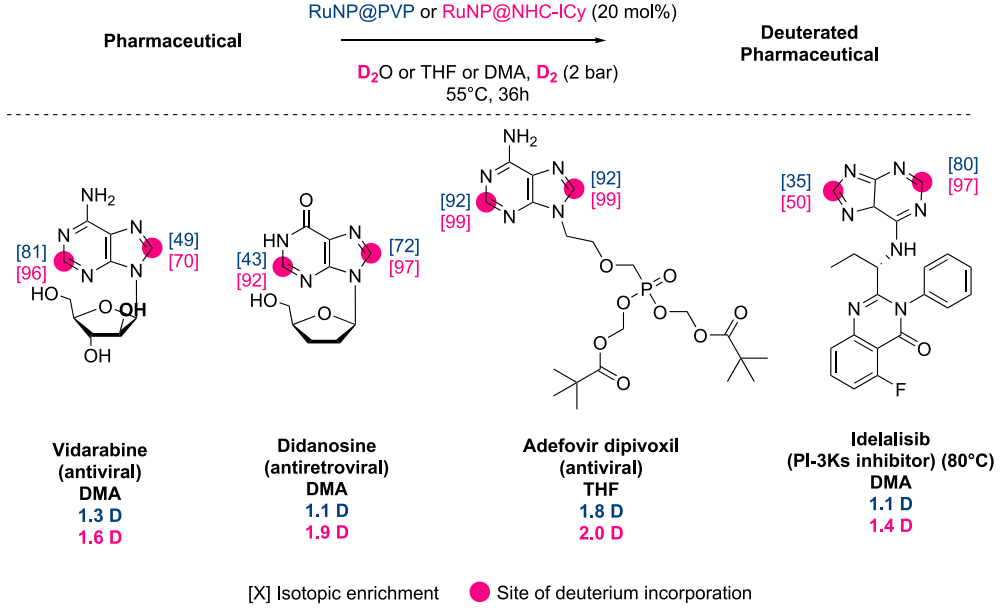

Figure 8. Deuterium labeling of pharmaceuticals. In blue, isotopic enrichment obtained with RuNP@PVP, and in pink with RuNP@NHC-ICy.

organic and aqueous media. Using RuNPs stabilized by organosoluble NHCs as opposed to RuNP@PVP led to faster deuteration kinetics for C(sp^2)−H bonds (see Figure 8). Furthermore, the higher metal content of the carbene-containing nanoparticles facilitated both workup and product purification, which is a crucial prerequisite for the method extension to tritium labeling.

In order to obtain good deuterium enrichment for oligonucleotides, we used RuNPs accommodating hydrosoluble NHC carbenes (NHC-PriPr) as ligands, displaying a very similar size and shape to the organosoluble ones. We achieved with these NPs the deuteration of 6- and 12-mer oligonucleotides with an average deuterium atom uptake of, respectively, 5.5 and 7.7 D (see Figure 9) after three iterative runs of catalysis. The viability of these molecules for SILS purpose in metabolomics and proteomics was confirmed when the relationship between the labeled/unlabeled MS intensity ratio and the oligomer concentration was found linear over at least 2 orders of magnitude (0.56−56 μM in the case of the 6-mer compound).

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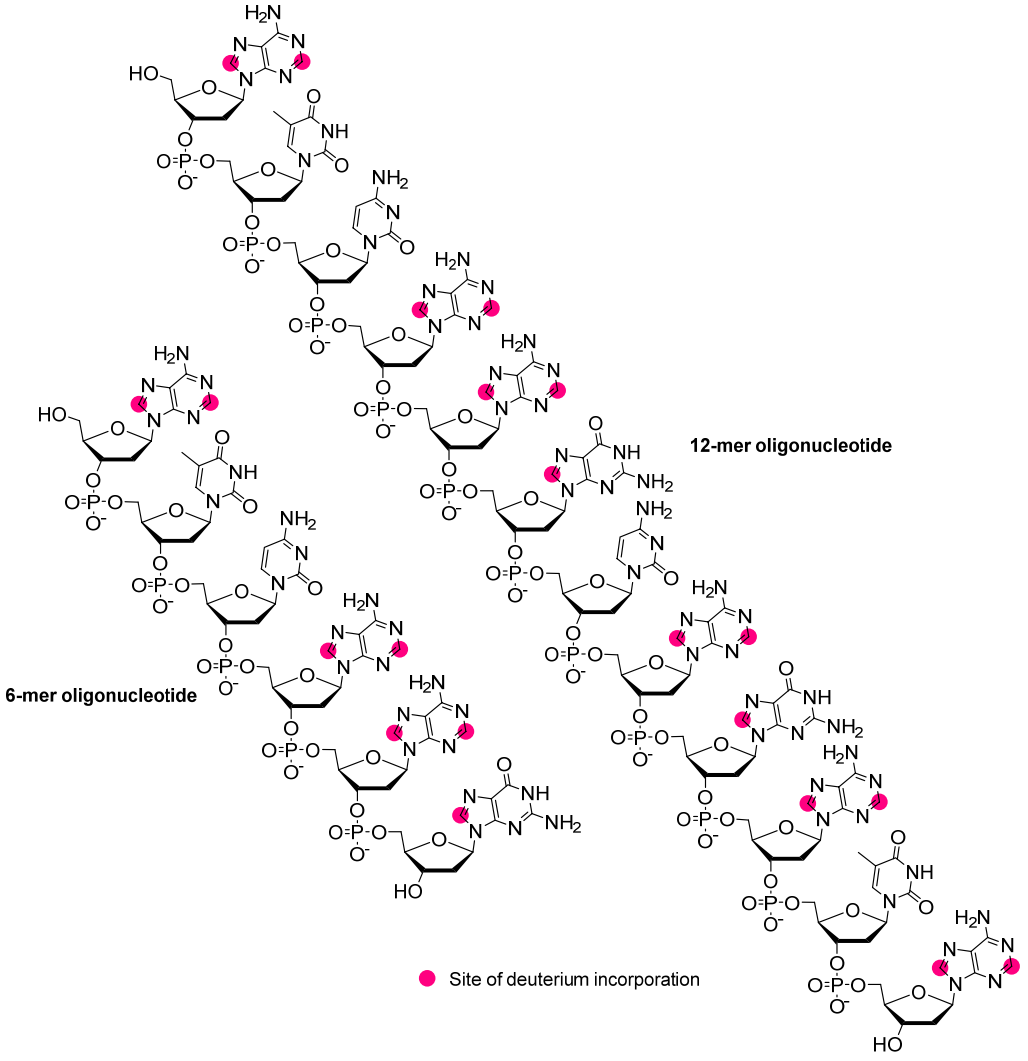

Figure 9. Structures of the labeled oligonucleotides and regioselectivity of the labeling.

3. NANOCATALYZED C(sp^3)–H ACTIVATION USING RUTHENIUM NANOPARTICLES

As shown in the introduction, C(sp^3)–H deuteration is achievable using RuNPs, but challenges persist in performing the reaction in water at different pHs and in controlling the stereochemical outcome when the deuteration occurs on stereogenic centers.

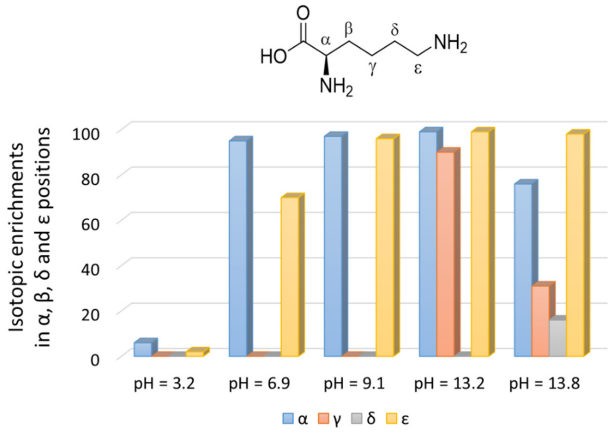

Figure 10. Isotopic enrichments in α, β, δ, and ε positions depending on the pH of the solution.

To study the pH dependence of the catalytic process in water, the selectivity of lysine deuteration as a function of pH was evaluated using either RuNP@PVP or RuNP accommodating hydrophilic carbenes as catalysts.[16] At acidic pH, the two amino groups are protonated and do not bind to the NPs, whereas at basic pH (13), the two amino groups are deprotonated and may be chelating on the NP. This translated into low isotopic enrichments up to pH 4, effective deuteration of the α and ε position near pH 7, with a preference for the α position, and deuteration of α, γ and ε positions, with a minor deuteration of the δ position at pH 13 (see Figure 10).

Here, the H/D exchange reaction can be directly monitored by NMR using the chemical shift perturbation technique, which allows for the determination of the nature of the chemical groups coordinated to the surface of the NPs. This technique confirmed that the deprotonated groups were coordinating to the surface of the NPs, and showed that at pH 7 the amino group of the alkyl chain, although protonated, underwent a dynamic exchange with surface deuterides.

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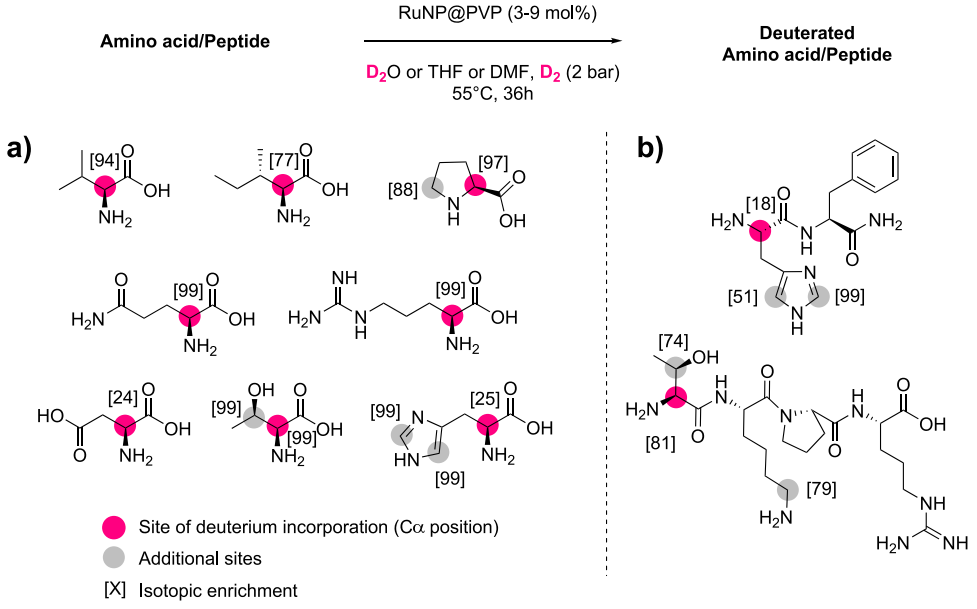

Figure 11. Enantiospecific C−H activation/deuteration of (a) amino acids and (b) biologically active peptides.

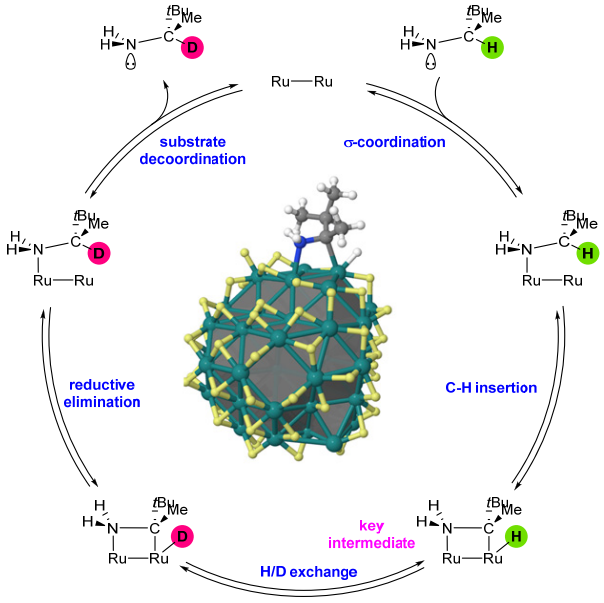

Figure 12. General mechanistic pathway for the enantiospecific α-deuteration of chiral amines using RuNP.

The labeling of chiral amines was achieved using RuNP@PVP as the nanocatalyst in 70−80% yields, with high isotopic enrichments (99%) and full retention of configuration suggesting an enantiospecific C−H activation process.[27]

As deuterated amino acids are essential substrates, for mechanistic studies of biochemical processes[28] or in metabolomics,[29] methods have been developed such as multistep synthesis[30] or through direct isotope incorporation. However, these either have a limited scope,[31] require the use of protecting groups,[32] or require protic solvents, thus preventing their use for tritiation experiments.[33]

Using Ru nanocatalysis in water, we were able to perform the efficient deuteration of amino acids bearing aliphatic (Ala, Val, Leu, Ile), amide (Asn, Gln) and nitrogen-containing (Pro, Arg, Lys) side chains along with hydroxyl-containing amino acids (Ser, Thr) where a labeling at the α-position relative to the oxygen was also observed. The labeled products were obtained with full enantiospecificity and good regioselectivity, regardless of the solvent used (THF, DMF, or heavy water). Applying this method to more complex and biologically active peptides, we managed to obtain substantial and regioselective deuterium incorporation without any detectable epimerization, thus demonstrating its usefulness for the late-stage deuteration of complex peptides (see Figure 11).

Theoretical calculations were also performed in order to investigate the mechanism and explain the observed enantiospecificity and regioselectivity. The mechanistic pathway is very similar to the α-deuteration of N-heterocycles previously discussed (see Figure 12). While the regioselectivity can be explained by a four-membered dimetallacyclic key intermediate, the retention of configuration might be due to the rigidity of the dimetallacycle and a rapid and barrierless H/D exchange process, taking advantage of the high mobility and diffusion of the hydrides/deuterides at the surface of the RuNPs. Interestingly, this theoretical study also suggests that deuteride diffusion may favor the HIE by significantly lowering the activation energy of the C−H insertion step, allowing the active metal center to keep its formal oxidation state.

In the context of the regioselective deuteration of amino acids, we have also investigated the use of bimetallic nanoparticles.[34] Even if only a slight change in selectivity for lysine deuteration was evidenced with different ratio of metals for RuPt nanoparticles, this opens the door to the potential beneficial use of bimetallic systems to increase the regioselectivity such HIE reaction.

4. NANOCATALYZED C(sp^2)−H AND C(sp^3)−H ACTIVATIONS USING Ru/C CATALYSTS

Thioethers are challenging to label by metal-mediated HIE because sulfur atoms are well-known to poison noble metal catalysts.[35] Therefore, despite their presence in a large number of pharmaceuticals and biomolecules, no general

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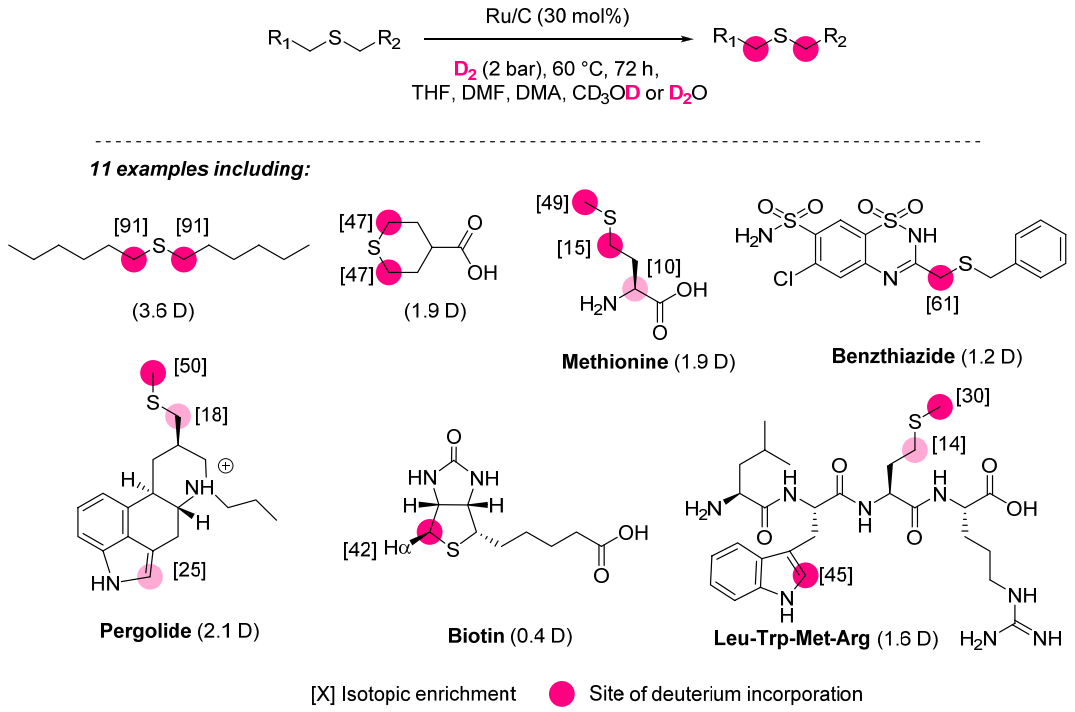

Figure 13. Deuterium labeling of sulfur-containing compounds using Ru/C (30 mol %) and D_2 gas (2 bar).

HIE method was described before we try to tackle this challenge using nanocatalysis. Using dihexylsulfide as a model substrate to screen the reactivity of different metallic NPs,[36] we found that using a large catalytic amount of Ru/C (30 mol %) in THF under a pressure of 2 bar of D_2 gas allowed the labeling at the α-position of the sulfur atom with high isotopic enrichment ([91]). Using this method, 11 complex molecules (amino acids, peptides, and drugs) containing a thioether moiety were labeled with good regioselectivities and moderate levels of isotope incorporation (see Figure 13).

The proposed mechanism may involve the formation of a rigid 4-membered dimetallacycle where the sulfur atom coordinates to the ruthenium surface. Running such a reaction at a larger scale has allowed evidence that a C−S bond cleavage can also occur, leading to the formation of MeSD. These species can poison the catalyst, which could explain the high catalyst loading needed and the rather moderate isotopic enrichment obtained for some substrates. Nevertheless, the deuterium enrichment can be increased by simply reiterating the catalytic process in order to prepare SILS. For instance, 4.1 deuterium atoms were incorporated in pergolide (a dopamine receptor agonist used for the treatment of Parkinson's disease) after three successive runs.

Despite its practical advantages (commercially available and air stable), ruthenium on carbon is also known to be able to reduce moieties such as aromatic rings or unsaturated heterocycles and bonds under a deuterium atmosphere. The competition between the reductive deuteration and the HIE can be to the disadvantage of the latter. Therefore, efforts have been made by our teams to modulate the reactivity of Ru/C by the addition of ligands. NHC ligands were chosen because they are capable of efficiently tuning the reactivity of homogeneous catalysts,[37] but also of heterogeneous catalysts as recently shown by the group of Glorius in the context of hydrogenation reactions.[38−40] The addition of various amounts (0.1−1 equiv vs Ru) of NHC ligands on Ru/C improved the selectivity of HIE over reduction for a wide range of sensitive compounds with high regio- and chemoselectivities (see Figure 14).[3]

The modified ruthenium catalysts were first applied to the deuteration of alcohols, and the best regioselectivity at the α-position of the oxygen atom of dodecanol was obtained with IAd(0.1 equiv)@Ru/C, a Ru/C catalyst with 0.1 equiv of NHC IAd ([*N*,*N*′-bis(1-adamantylimidazol)-2-ylidene]). In this case, the ligand modification slightly improves the regioselectivity of the deuterium incorporation. A more impressive switch of reactivity between commercially available Ru/C and modified Ru/C was observed regarding easily reducible phenyl derivatives such as benzoxazole, phenylpyridine, oxazole derivatives, and quinoline. In all cases, high chemoselectivities were observed toward the C−H deuteration versus the reductive deuteration process (see Figure 15). For quinoline, Ru/C gave only the reductive product whereas a 96% yield of the labeled quinoline was obtained with IAd(1 equiv)@Ru/C in THF at 55 °C and under a pressure of 1 bar of D_2 gas, hence demonstrating the efficiency of the modified catalyst to favor labeling over reductive reactions. Similarly, applying modified catalysts for the labeling of aldehyde moieties gave access to C-1 deuterated compounds instead of reduced ones (see Figure 14). Indeed, five aldehydes were deuterated using IAd(1 equiv)@Ru/C, with a deuterium incorporation up to 78% and yields up to 86%, whereas only alcohols as the reduced products were produced using native Ru/C as catalyst.

This switch of reactivity was explained by the incorporation of bulky ligands at the surface of the ruthenium catalyst. Indeed, IAd ligands coordinate strongly to the surface of the Ru cluster, thus reducing the available number of binding sites for substrate coordination. Thus, the π-coordination necessary for the reductive deuteration becomes more difficult than the σ-coordination of a nitrogen or an oxygen atom directing the C−H activation (see Figure 16).

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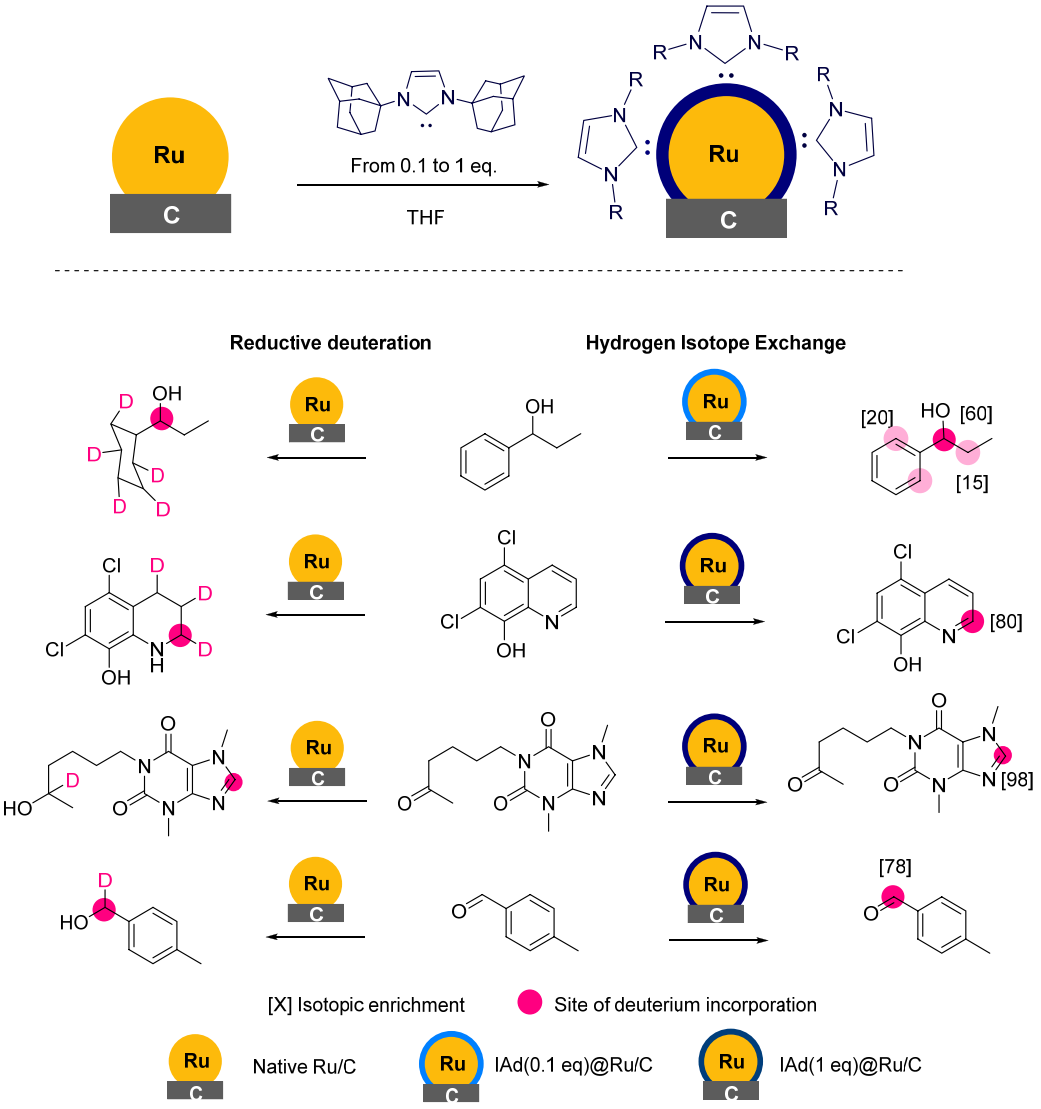

Figure 14. Synthesis of modified Ru/C catalysts and comparison of the deuterium labeling with Ru/C and IAd@Ru/C.

Control experiments showed that the rate of the reductive deuteration was therefore lowered compared to the rate of the deuterium labeling. This study demonstrated the great potential of the addition of organic ligands at the surface of nananocatalyst to tune both the regio- and chemoselectivities of heterogeneous catalysts and nanoparticles in the context of C−H activation reactions.

5. NANOCATALYZED C(sp^2)−H ACTIVATION OF REDUCIBLE FUNCTIONS USING IRIDIUM NANOPARTICLES

Ruthenium nanoparticles have proved their efficiency and versatility in HIE reactions but have also demonstrated limits such as competition with reductive deuteration on easily reducible substrates. Therefore, other metal-based catalysts were envisioned for the labeling of reducible compounds such as aniline, and iridium, particularly well-known in homogeneous catalysis for HIE reactions since the discovery of Crabtree's catalyst in 1979, seemed a good choice for this investigation.[41] A plethora of iridium catalysts have been described for the homogeneous labeling of heterocycles and pharmaceuticals, and some of them are commercially available such as Kerr's or Burgess' ones.[42−45] These iridium catalysts are known to perform labeling at the *ortho* position of a directing group through 5- or 6-iridacycles, and labeled compounds can be obtained with very high efficiency and regioselectivity.[46] Surprisingly, the use of iridium heterogeneous catalysts or nanoparticles was scarcely reported in the context of HIE.

In collaboration with Derdau et al., we have synthesized iridium nanoparticles starting from the commercially available $[Ir(COD)(OMe)]_2$ (COD = 1,5 cyclooctadiene) precursor and ICy (cyclohexyl) as ligands (0.125 equiv) under 5 bar of H_2 gas at room temperature.[47] These very small air-stable NPs of 1.2 nm (mean size) were first tested in HIE reactions on anilines. Anilines are essential substructures in drugs, but no efficient and general methods using D_2 or T_2 as isotopic source have been described so far to gain access to deuterated or more complex tritiated anilines with high isotope incorporation along with a high degree of compatibility regarding sensitive functional groups. Using mild conditions, iridium NPs catalyzed the HIE on simple anilines, leading to high isotope incorporation at the *ortho* position of the amino function (see Figure 17), while

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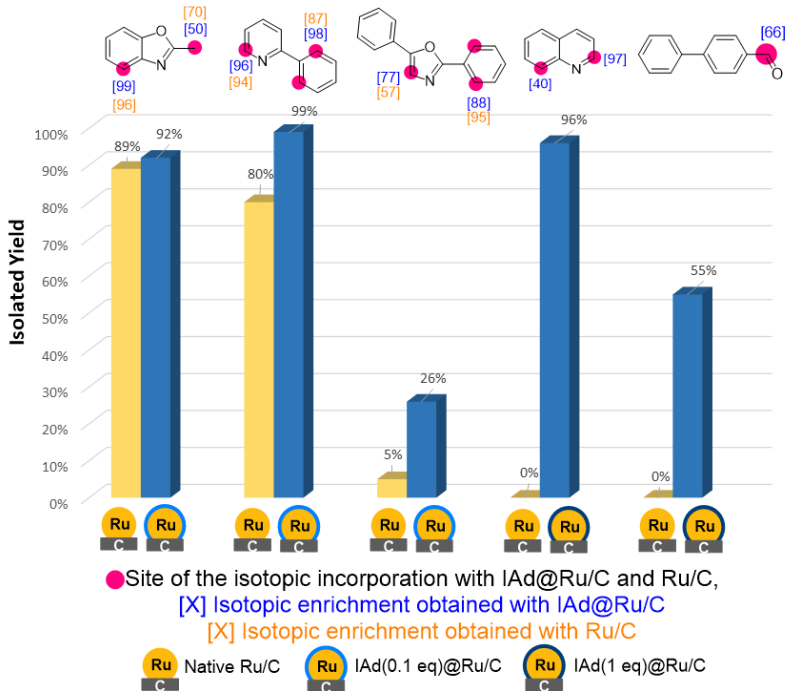

Figure 15. Deuterium labeling of reducible functions and comparison of reactivity between commercial Ru/C and modified Ru/C.

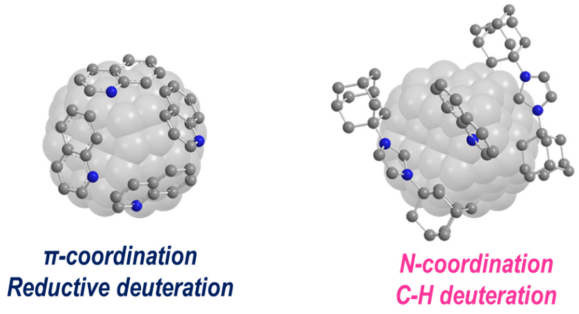

Figure 16. Schematic representation of the coordination of quinoline depending on the nature of the Ru catalyst: Native Ru/C catalyst on the left (π-coordination) and NHC modified catalyst on the right (N-coordination).

ruthenium nanoparticles led mainly to the reduction of the substrate.

Furthermore, this method is compatible with diverse functional groups such as halogens (fluorine, bromide), alcohols, ketones, or esters, thus paving the way to more complex structures. Application to anilines of higher polarity led to moderate deuterium enrichments with iridium nanoparticles in THF. Heating to 80 °C and adding D_2O as cosolvent led to improved incorporations. These reaction conditions were applied to five aniline-containing pharmaceuticals with success (Figure 18).

Their ability to activate C−H bonds in complex molecules with a high functional group tolerance and their lower activity in terms of reductive deuteration compared to RuNPs suggests the high potential of IrNPs as catalysts in the context of HIE.

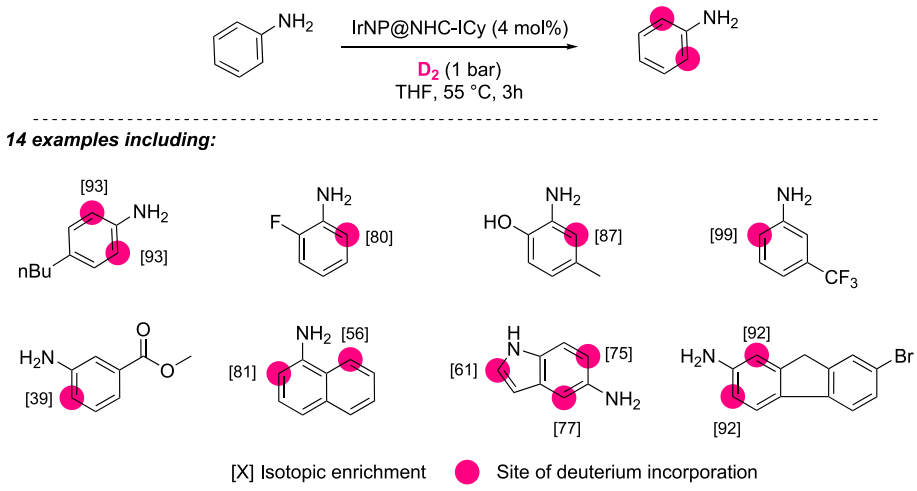

Figure 17. Deuteration of anilines with iridium nanoparticles in THF under D_2 gas.

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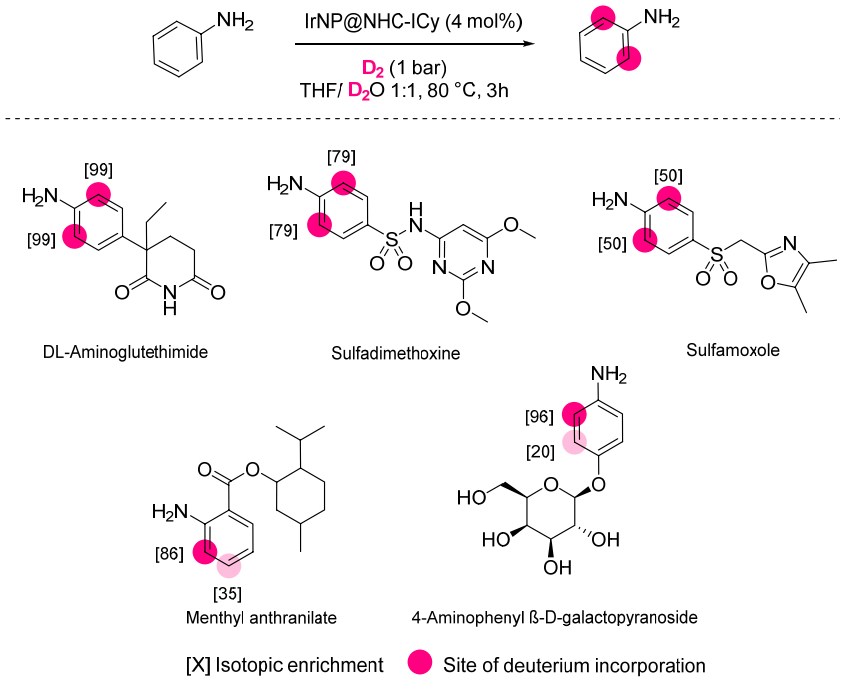

Figure 18. Deuteration of pharmaceuticals with iridium nanoparticles in THF/D_2O under D_2 gas.

Table 1. Nanocatalyzed Deuteration of Heterocycles ($C(sp^2)$–H Activation Mainly)

Substructure	Labeling positions (depending on substitution pattern)	**Catalyst** & chemoselectivity & Functional Group Tolerance (FGT)	Substructure	Labeling positions (depending on substitution pattern)	**Catalyst** & chemoselectivity & Functional Group Tolerance (FGT)
Pyridine		**RuNP@PVP**: Reduction observed for some substrates **NHC@Ru/C**: Limited reduction FGT: OMe, OH, NR_3, amide,...	Benzimidazole		**RuNP@PVP** FGT: OMe, amine, F, NH2
Quinoline		**RuNP@PVP**: High amount of reduction **NHC@Ru/C**: Limited reduction FGT: OMe, OH, Cl, amide,...	Oxazole		**RuNP@PVP** FGT: OMe, COOH, NH_2
Indole		**RuNP@PVP** FGT: OMe, amide *Higher isotopic enrichment and regioselectivity might be observed with the addition of Cs_2CO_3*	Purine		**RuNP@PVP** & **RuNP@Ipr**: Water soluble substrates **RuNP@ICy**: Organosoluble substrates FGT: OMe, COOH, NH_2 *Labeling of complex oligonucleotides*
Carbazole		**RuNP@PVP** + Cs_2CO_3 (1eq) FGT: OMe, amine, Boc, OH	Triazole		**RuNP@PVP** FGT: OMe, amide, NH_2, F, Cl, OH
Imidazole		**RuNP@PVP** FGT: OMe, amine, Boc, OH	Aniline		**RuNP@ICy**: Full reduction **IrNP@ICy** FGT: OMe, ester, amide, NH_2, F, Cl, CF_3, OH

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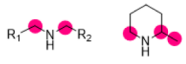
Table 2. Nanocatalyzed C(sp^3)−H Deuteration of Amines, Thioethers, and Alcohols and C1 Deuteration of Aldehydes

Substructure	Labeling positions (depending on substitution pattern)	**Catalyst** & chemoselectivity & Functional Group Tolerance (FGT)
Primary amine and amino acid 		**RuNP@PVP**: Reduction observed for phenylalanine FGT: OMe, OH, COOH, amide, *Enantiospecific labeling with retention of configuration*
Secondary amine 		**RuNP@PVP** FGT: OMe, OH, Cl, amide, F, alkene,...
Tertiary amine 		**RuNp@PVP** FGT: OMe, amide
Thioether 		**Ru/C:** Desulfuration reaction limiting isotopic enrichments FGT: OMe, NR_2, COOH, Cl, amide, SO_2NHR, urea, indole
Alcohol 		**NHC@Ru/C** FGT: OMe **Ru/C**: Unselective labeling **RuNP@PVP**: Decarbonylation
Aldehyde 		**NHC@Ru/C** FGT: ether, amide, NMe_2 **Ru/C and RuNP@PVP**: Reductive deuteration yielding to the corresponding deuterated alcohol

In brief, Tables 1 and 2 compile the regioselectivity of the isotope incorporation by substructures, depending on the nature of the nanocatalysts, the functional group tolerance experimentally validated (FGT), and the comments about selectivity issues.

6. NANOCATALYZED HYDROGEN TRITIUM EXCHANGE

As explained in the Introduction, tritium labeled molecules are of paramount importance in the drug discovery process: they are used for autoradiography or in radioligand binding assays, and they can act as radioactive tracers for *in vivo* fate studies.[7] For these purposes, labeled compounds need to be obtained with a high level of isotope incorporation (around 10−15 Ci·mmol^{-1} for most of their applications but up to a minimum of 50 Ci·mmol^{-1} for their use in binding assays). Nanocatalyzed HIE seems suitable for tritium labeling because it may allow the late-stage incorporation of tritium atoms in only one step, leading to compounds with sufficient molar activity and limiting radioactive waste, time, and costs spent for the long synthetic sequences. In addition, heterogeneous catalysts and nanoparticles are easy to remove by simple filtration, facilitating the purification process. Regarding the isotopic source, D_2 gas is easily replaced by T_2 gas, which is the isotopic source of choice since it is by far the easiest accessible raw material.

Methods developed were applied to the tritiation of biologically relevant compounds under the same reaction conditions except for the use of higher catalytic loadings and a subatmospheric pressure of T_2 due to safety and regulatory issues and to limit the generation of radioactive wastes.

Using RuNP@PVP, we successfully performed the labeling of three main scaffolds: benzimidazole (astemizole), 1,2,4-triazole (fluconazole), and carbazole (protected carvedilol). Molar activities up to 24.7 Ci·mmol^{-1}, in accordance with the prerequisites for ADME studies (see Figure 19), were obtained using low T_2 gas pressure (0.5−0.9 bar).[23] Following our NP engineering studies, organosoluble RuNP@NHC-ICy was used to achieve the tritiation of didanosine (an antiretroviral agent) and idelalisib (used for the treatment of blood cancer), obtained with good molar activities (>23 Ci·mmol^{-1}).[2] Pergolide, a sulfur-containing compound, was also tritiated with a molar activity of 15 Ci·mmol^{-1} under similar conditions using Ru/C.[36] Finally, iridium nanoparticles were used for the tritiation of the volixibat pharmacophore, and the drug was efficiently labeled with a molar activity of 25 Ci·mmol^{-1}, in accordance with the result obtained in the deuteration processes.[47]

However, despite their numerous advantages, the use of nanoparticles for tritiation experiments can be limited by (i) the need of strict anhydrous conditions, as they can catalyze the T_2/H_2O exchange, thus diluting the isotopic source; (ii) the possible formation of byproducts coming from a reductive pathway when the substrate is easily reduced (e.g., quinoline); (iii) the need for a T_2 gas pressure above 500 mbar when many homogeneous catalysts are able to perform labeling reactions under a pressure of 200 mbar or even less,[17,18] thus limiting their application in some radiolabeling laboratories; (iv) the possible location of the tritium label on metabolically unstable positions which would not, however, limit its use as radioligands. Nevertheless, we strongly think that the aforementioned advantages of using NP outweigh these weaknesses and we are still working on the development and improvement of new catalysts.

Hence, investigations were carried out to try to overcome some of the mentioned drawbacks. We discovered that the commercially available and air-stable $[Ir(COD)(OMe)]_2$ used as precursor for the synthesis of the IrNPs was a powerful precatalyst for the labeling of a wide range of compounds.[4] Thus, the model substrate, 2-phenylpyridine, was labeled both at the *ortho* position of the phenyl ring as usually obtained using an homogeneous catalyst and at the pyridinic core as usually obtained using nanoparticles under mild conditions (THF at 55 °C and under 1 bar of D_2 gas), leading to multiple sites deuterium labeling.

This multiple site C−H bond activation led us to question the nature of the active species. TEM and HR-TEM experiments, as well as mass spectrometry measurements, revealed the presence of at least two types of catalytic species formed *in situ*: Ir nanoparticles and homogeneous Ir complexes. Therefore, we concluded that iridium nanoparticles are formed *in situ* during the reaction and are responsible for the labeling of positions not accessible by homogeneous catalysis. Encouraged by this discovery, which can lead us to the maximization of the hydrogen isotope incorporation and therefore to applications requiring high molar activities or isotopic enrichments, the scope of the reaction was evaluated. A large number of structures (pyridine, oxa- and thiazoles, carbazole, indole) were deuterated with very high levels of isotope incorporation and with a high tolerance toward sensitive functional groups (nitrile and halogen atoms: Br, Cl, and F). We then turned

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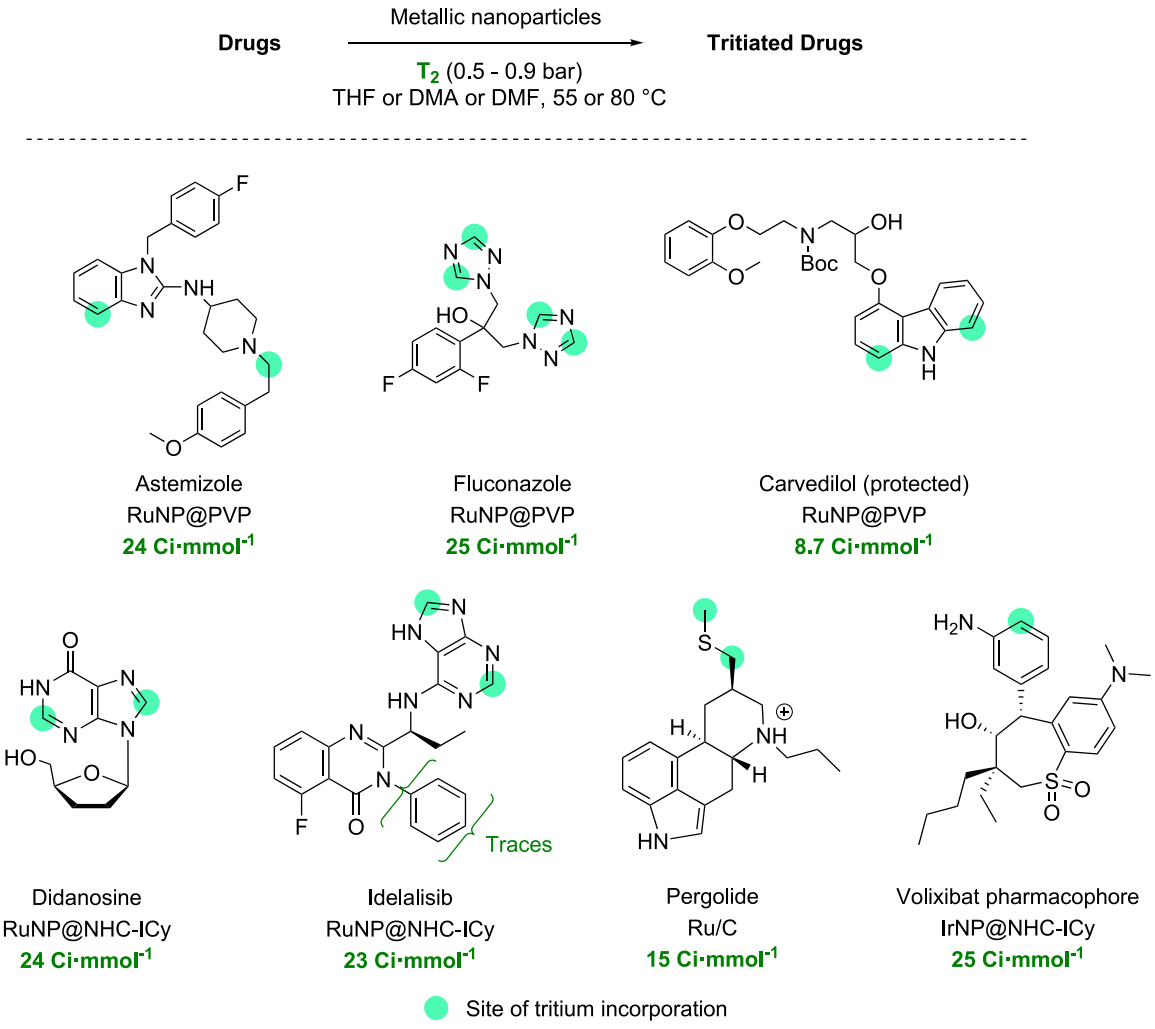

Figure 19. Tritium labeling of complex pharmaceuticals using metallic nanoparticles.

our attention to pharmaceuticals, which also gave high degrees of deuteration incorporation across multiple sites.

This method showed promising advantages for the tritiation of pharmaceuticals: the catalyst is easy to handle, the tritium source is T_2 gas, and thus high isotope incorporation would be expected. Therefore, we performed the tritiation of seven pharmaceuticals of interest, and the reactions gave, as expected, tritiated molecules with high molar activities (see Figure 20). Bisacodyl was, for instance, obtained with a molar activity of 122 Ci·mmol^{-1}, thus greatly exceeding the values obtained by previously described methodologies.

7. CONCLUSION AND PERSPECTIVES

The results summarized in this Account illustrate the usefulness of Ru and Ir nanoparticles to catalyze hydrogen isotope exchange reactions. Notably due to the polymetallic nature of their surface and the surface hydride mobility, Ru and Ir NPs are able to activate a broad variety of C−H bonds in complex molecules followed by either deuterium or tritium incorporation in the presence of D_2 or T_2 gas within low energy barriers. Their great solvent tolerability allied with the possibility to perform multiple isotope incorporation using mild reactions conditions makes this approach complementary to the use of homogeneous catalysts to synthesize complex labeled molecules. Our recent contributions also highlight the interesting perspectives offered by (1) the possibility to increase the regio- and chemoselectivities of such nanocatalysts (or heterogeneous catalysts) by adding organic ligands (e.g., NHC) at their surface; (2) the *in situ* formation of metallic nanoparticles allowing to perform multiple site HIE using easy-to-implement synthetic methods.

On the fundamental viewpoint, HIE reactions evolved as an interesting tool to monitor the impact of nanoparticles engineering on their catalytic activities (regioselectivity, chemoselectivity, kinetics, for instance) in the context of C−H activation reactions. On a more applicative viewpoint, the discovery of novel well-defined nanoparticles or organometallic precursors allowing the *in situ* formation of nanoclusters, involving non-noble metals (Ni,[48] Fe, ...), and owning good performances in HIE reactions would be highly desirable and are currently under investigation.

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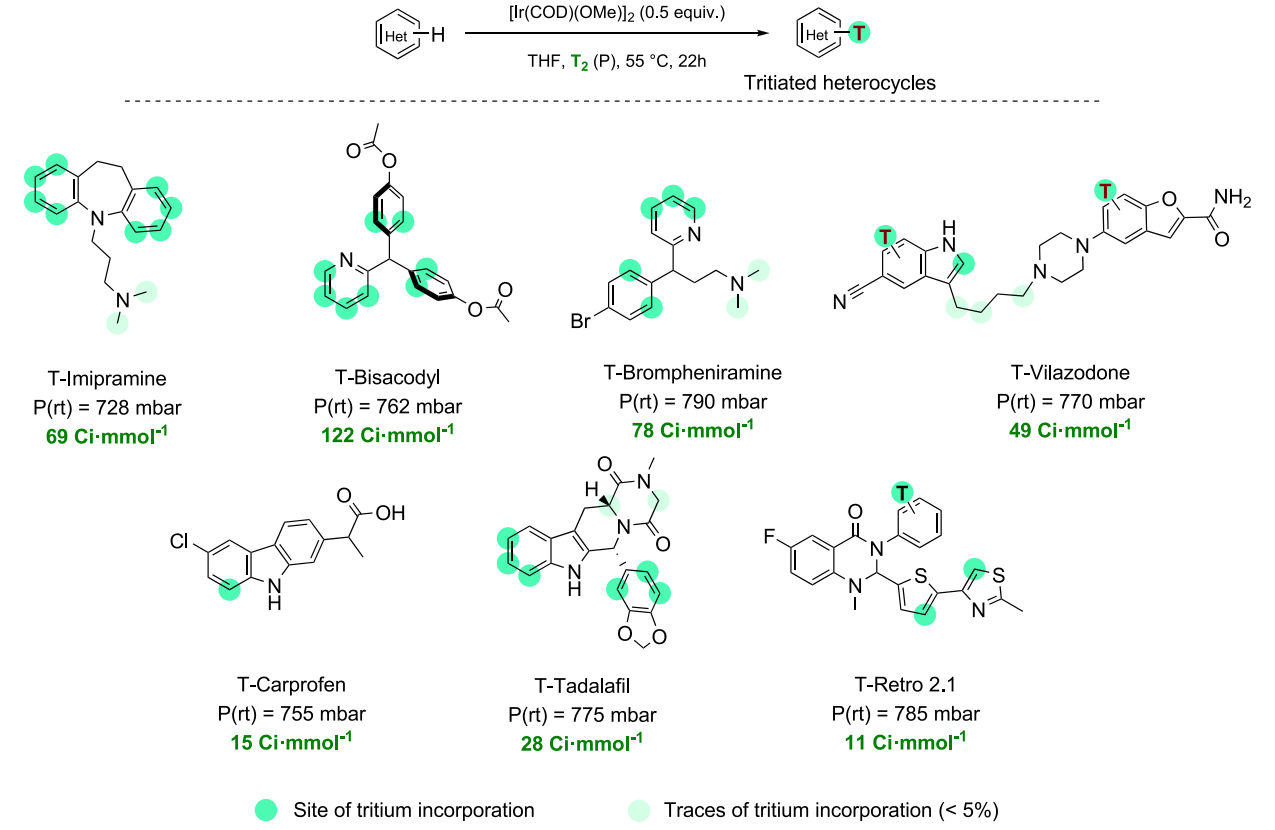

Figure 20. Tritiation of complex pharmaceuticals with $[Ir(COD)(OMe)]_2$ in THF under T_2 gas subatmospheric pressures.

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Author Contributions

M.L. and M.D.-B. contributed equally. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

Biographies

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Gabriel Mencia (28/11/1992, Spain) obtained his degree in chemistry from the University of Alcalá (Spain) and started his PhD degree in 2015 at the University of Alcalá (Gomez group). Since 2020, he is a postdoctoral research scientist at the LPCNO of Toulouse under the supervision of Dr. Chaudret.

Bruno Chaudret (25/12/1953, France) graduated from École Nationale Supérieure de Chimie de Paris in 1975. He received his PhD from Imperial College London in 1977 with Sir Wilkinson and the degree of a "Docteur és Sciences" from the University of Toulouse in 1979. He is now "Director of Research CNRS" and Director of the "Laboratoire de Physique et Chimie des Nano-Objets" in Toulouse and is a member of the French Academy of Science and of Academia Europeae.

Sophie Feuillastre (13/07/1987, France) obtained in 2014 her PhD degree from Université Lyon 1, France (Pr. Piva's group). She moved next to the CEA as a postdoctoral fellow (2014−2016). After working for a SME supplier in Europe of stable isotopes, as the

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main leader and senior scientist, she held in 2016 a permanent position at the CEA as a researcher in the tritium laboratory.

Grégory Pieters (03/05/1983, France) obtained his PhD from Université de Versailles Saint-Quentin-en-Yvelines (France) in 2010 (Prim group). After a postdoctoral experience at University of Padova (Prins group, until june 2012), he integrated CEA Paris-Saclay first as a postdoctoral fellow (Rousseau group, until June 2013) then as a permanent researcher. In 2017, he obtained the agreement to supervise research (HDR) and became group leader at the tritium laboratory.

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■ ABBREVIATIONS

HIE, hydrogen isotope exchange; NP, nanoparticles; PVP, polyvinylpyrrolidone; NHC, N-heterocyclic carbenes; DMA, dimethylacetamide; COD, cyclooctadiene

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